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Exhibit A
to the Declaration of
Lawrence C. SMITH

Attorney Docket No. : 10662-86US MG/lyl

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Lawrence C. SMITH EXAMINER: D. CROUCH

SERIAL NO. : 10/019,375 ART UNIT: 1632

FILED : March 5, 2002

FOR : TELOPHASE ENUCLEATED OOCYTES FOR NUCLEAR TRANSFER

* * * * *

DECLARATION OF Dr. Lawrence C. SMITH, Ph.D.

I, Lawrence C. SMITH hereby declare and say:

1. I am a citizen of Canada, presently residing at 2950, Lafontaine, Saint-Hyacinthe, Québec, Canada.

2. I am scientific researcher in the Animal Reproduction Research Centre of the "UNIVERSITÉ de MONTRÉAL", the owner of the above-identified patent.

3. That my academic background and experiences in the field of the present invention are listed on the enclosed *curriculum vitae*.

4. I am the inventor in the present application and have read and understand the specification.

5. That the following experiments were conducted to demonstrate the method of the present application.

Production of cloned live born bovine offsprings

Method of preparing nuclear donor cells for cloning at G1-phase of the cell cycle (G1-phase donor cells used with metaphase oocytes)

Fetal or adult skin-derived fibroblasts were obtained from tissue biopsies and cultured in DMEM™ medium supplemented with 10% FCS. Proliferating cells were passed once and aliquoted for freezing at a second passage. Frozen cells were thawed and plated at 10,000 cells/ml in plastic culture dishes with 6-cm diameter. After 3 days of culture cells reached confluence and were used for nuclear transfer 2-4 days after attaining confluence. Flow cytometry analysis showed that approximately 95 % (96-98% for fibroblasts and 93-96% for granulosa cells) of the cells are at the G1/G0-phase at 48 h of culture in confluence. The developmental potential of embryos produced by nuclear transfer was compared between cells synchronized by confluence and those synchronized by serum starvation (5 days of culture in DMEM™ medium supplemented with 0.5% of FCS). Development to blastocyst stage after 7

days in culture was similar between cells synchronized by confluence and serum starvation when using fetal (19 vs. 22 %) and adult (26 vs. 27%) fibroblasts.

Metaphase-stage oocyte enucleation

Follicles with 2 to 8 mm diameter were aspirated from bovine slaughterhouse ovaries. Oocytes with a homogeneous cytoplasm and several layers of cumulus cells were selected and placed in maturation medium. At 22 h after maturation oocytes were denuded of cumulus cells and those with a first polarbody were used in the experiment. Selected oocytes were placed in medium containing cytochalasin B (5µg/ml; micromanipulation medium) and the first polarbody and the surrounding cytoplasm were aspirated. Exposure to a vital dye (Hoechst 33342) and ultraviolet light indicate that 60 to 70% of the oocytes did not contain meiotic chromosomes, i.e., were enucleated, after the aspiration procedure. Enucleated oocytes are returned to maturation medium for a further 6 h until nuclear transfer. After this period, a single donor cell was introduced into the perivitelline space and electrofused by exposure to a 1.5 KV/cm electric pulse lasting 70 µsec. After electrical stimulation, oocytes are washed, placed cultured medium for another 1-2 h and examined for fusion. Fused couplets derived from metaphase-stage enucleated oocytes were placed in medium containing 5 µM ionomycin to induce activation. No inhibitors of protein synthesis or kinase activity were used after activation with ionomycin.

Method of preparing nuclear donor cells for cloning at G2/M-phase of the cell cycle (G2/M-phase donor cells used with telophase oocytes)

Confluent donor cells were plated at 10,000 – 20,000 cells/ml in DMEM medium with 10 % of FCS and cultured for 16 to 24 h before use in nuclear transfer. Flow cytometry assessment indicated that 45-75 % of cells was at S phase at 16 h and 20-55% was at G2-M phase at 24 h after plating. Nuclear transfer was performed with cells at 16 to 24 h post plating and development to blastocyst stage were 24% using pre-activated telophase-II enucleated oocytes compared with 11% for M-II enucleated oocytes. Inhibiting entry into mitosis with specific (roscovitine) or non-specific (6-DMAP) kinase inhibitors can increase the percentage of cells at G2/M-phase.

Telophase-stage enucleated oocytes

Follicles with 2 to 8 mm diameter were aspirated from bovine slaughterhouse ovaries. Oocytes with a homogeneous cytoplasm and several layers of cumulus cells were selected and placed in maturation medium. At 28 h after maturation oocytes were denuded of cumulus cells

and those with a first polarbody were used in the experiment. Oocytes were exposed to 5-μM ionomycin and cultured for a further 2 h. Oocytes with expelling or expelled second polarbodies were enucleated at telophase II-stage by removing approximately one-tenth of the cytoplasm adjacent to the second polar body. Nuclear donor cells were injected into the perivitelline space and fused to the telophase-enucleated host cytoplast at approximately 2.5-h after activation.

Chemically defined medium for culturing *embryos in vitro*

Embryo culture medium

Serum is often added to *in vitro* culture systems as a source of the necessary nutrients and growth factors that lack in balanced salt solutions. However, because of its unknown and variable composition, the use of serum in culture media during the early stage of embryo development has been directly related with abnormal growth patterns in both cattle and sheep. Therefore, development of chemically defined *in vitro* culture systems that lack serum are of great interest for many embryo biotechnologies that require exposure to *in vitro* environments, including mammalian adult cloning. Apart from the correct balancing of minerals in culture media, energy and amino acid composition, and the concentration of oxygen in the atmosphere seem to play an important role in supporting early development.

Experiments to test Embryo Culture Medium

All cultures used tested using *in vitro* matured and fertilized bovine zygotes (presumptive-zygotes) and were performed in 50 μl drops of medium under equilibrated mineral oil in 5% CO_2 at 38°C.

Experiment 1: Effects of glucose on development to the blastocyst stage

The control *in vitro* culture group was based on Menezo B2™ culture medium supplemented with 10% FCS in the presence of bovine oviductal cells at atmospheric (18%) oxygen levels. Our treatment groups were based on SOF medium modified by supplementing with 8 mg/ml of fatty acid-free BSA and 1 mM glutamine cultured in 5% oxygen. Treatment 1 contained 0.5-mM glucose and treatment 2 contained 1.5-mM glucose. The percentage development to the blastocyst stage was superior in 0.5-mM glucose medium (33%) when compared to 1.5 glucose (26%) and control (23%) media. These results indicate that lower levels of glucose (0.5 mM) support better *in vitro* development to the blastocyst stage.

Experiment 2: Effects of alanine and glycine at oviductal concentrations

Based on results from Experiment 1, the control *in vitro* culture group was based on the modified SOF medium containing with 0.5-mM glucose. In an attempt to simulate the amino acid concentrations present in the oviduct a treatment group was supplemented with 0.5-mM alanine and 1.5 mM glycine. Although no significant difference in blastocyst stage development was obtained at day 7 of culture (38 vs. 41%), significantly more blastocysts batched from the zona pellucida at day 9 when cultured with extra alanine and glycine than controls (75% vs. 47%). These results indicate that alanine and glycine at oviductal concentrations support better long-term development during culture *in vitro*, suggesting that embryos may produce higher gestation rates after transfer into the uteri of recipient females. The latter is supported by the production of a healthy somatic cell cloned calf derived using the above *in vitro* culture medium.

Method used to produce calves by somatic cell cloning

Method 1: Confluent donor cells with metaphase-arrested host oocytes

a) fibroblasts from the skin of a day 55 fetus are plated at 10^6 cell/ml in a 60 mm diameter dish in medium alpha-DMEM supplemented with 10% of fetal calf serum;

b)fibroblasts are cultured for 4 days at 38°C until cell cycle arrest by confluence inhibition (mostly at G1/G0 stage of the cell cycle);

c)confluent-arrested cells are trypsinized and used within one hour in nuclear transplantation experiments;

d)host oocytes were enucleated at metaphase-stage (M-II) at 22 h from the beginning of *in vitro* maturation (IVM), fused to at 26 h and activated at 28 h after IVM;

f) confluence-arrested fibroblasts were positioned within the perivitelline space of enucleated M-II oocytes and exposed to an electric current for fusion at 26 h after IVM;

g) at 28 h after IVM, reconstructed (fused) oocytes were exposed to 5 µM Ionomycin in TCM-199 hepes-buffered medium during 4 minutes;

h) reconstructed oocytes were cultured for 8 days in CRRA-modified SOF medium at 38.5 °C in an atmosphere of 5% CO_2 and 5% O_2.

i) blastocyst-stage embryos were transferred to synchronized recipient heifers and allowed to develop to term.

Method 2: Roscovitine-arrested donor cells with telophase-enucleated host oocytes

a) confluent-arrested fibroblasts (Method 1) were plated into dishes at low density and cultured for 20 h to enable initiation of cycling activity (most cells are in the S-phase of the cell cycle);

b) cycling cells exposed to roscovitine at 50 μM for 8 h, at which stage most cells are arrested at the G2/M phase of the cell cycle;

c) host oocytes were activated with ionomycin (as described in Method 1) at 28 h after IVM and enucleated and fused to roscovitine-arrested donor cells 2.5 h later;

d) reconstructed oocytes were cultured for 8 days in CRRA-modified SOF medium at 38.5 °C in an atmosphere of 5% CO_2 and 5% O_2.

e) blastocyst-stage embryos were transferred to synchronized recipient heifers and allowed to develop to term.

Results

Table 1

Preliminary results comparing the gestation outcome of embryos reconstructed using methods 1 and 2.

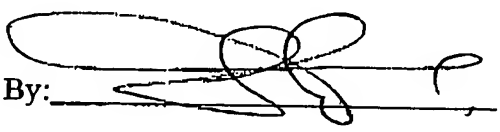
Method of	Recipients	Gestations (%)		
Reconstruction	Transferred	Day 30	Day 60	Births
Method 1	5	3 (60%)	2 (40%)	1 (20%)
Method 2	5	3 (60%)	3 (60%)	2 (40%)

Conclusion

These experiments were designed to prove that the quality of cloned embryos produced by the method of cloning are of quality higher than embryos produced by other methods. This is supported by the fact that higher yield of birth is allowed.

6. I declare further that all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

Date: June 3, 2005

By: 

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ADDRESS

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HIGHER EDUCATION

Ph.D.	Roslin Research Institute (Dr. I. Wilmut) and Department of Obstetrics and Gynecology (Dr. J.D. West), Faculty of Medicine, University of Edinburgh, Edinburgh, U.K.
M.Sc.	Department of Animal Genetics (Dr. W.G. Hill and Dr. J. Manson) Faculty of Science, University of Edinburgh, Edinburgh, UK
D.V.M.	Faculty of Veterinary and Agricultural Sciences, São Paulo State University (UNESP), Campus of Jaboticabal, São Paulo, Brazil.

EMPLOYMENT HISTORY

April 2004 – to date	Founding President and Senior Scientific Officer – Clonagen inc., Saint-Hyacinthe, QC Canada
Sept 2001 – to date	Chair in Animal Cloning and Biotechnology, Faculté de médecine vétérinaire, Université de Montréal, Saint-Hyacinthe, QC, Canada.
June 2001 – to date	Professor, Centre de recherche en reproduction animale (C.R.R.A.), Dept biomédecine vétérinaire, Faculté de médecie vétérinaire, Université de Montréal, St-Hyacinthe, PQ, Canada.
June 1995 – May 2001	Associate Professor, C.R.R.A., Dept. biomédecine vétérinaire, Faculté de médecie vétérinaire, Université de Montréal, St-Hyacinthe, PQ, Canada.

June 1992 - May 1995	Assistant Professor, C.R.R.A., Dept. biomédecine vétérinaire, Faculté de médecie vétérinaire, Université de Montréal, St-Hyacinthe, PQ, Canada.
May 1989 - June 1992	Research Associate, C.R.R.A., Dept anatomie et physiologie vétérinaire, Faculté de médecie vétérinaire, Université de Montréal, St-Hyacinthe, PQ, Canada.
Jan. 1985 - March 1985	Geneticist for Poultry and Porcine Breeding Programs Sadia Concordia S/A, Concordia, SC, Brazil.
July 1981 - Sept. 1982	Veterinarian and Herd Health Manager Arrossensal Agrop./Indust. S/A, Nortelândia, MT, Brazil.

PRIZES AND AWARDS

- Prix d'excellence Pfizer 1998 pour la recherche en santé animale;
- Chaire de recherche du Canada en Clonage et Biotechnologie Animale (since 2001);

PATENTS

Smith, LC, Bordignon, V. et Fortes Pontes, H. (2000) Déposée au Bureau de Brevets des Etats-Unis le 5 décembre 2000. Titre : « Method for cloning animals». PCT/020988;.

Smith, L.C. et Bordignon, V. (1999) Démande de brevet internationale "Telophase enucleated oocytes for nuclear transfer". No de la démande PCT/CA00/00483; Date de dépot international: le 27 avril 2000; Date de priorité américaine: le 28 avril 1999

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7. **Smith, L.C.** (2001) Nucleo-Cytoplasmic Interactions During Early Embryonic Development : Biotechnological Applications. In : Br. Monogr. Reprod, ed. A.A.R. Silva, Arte & Ciência, SP, pp. 175-180;
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9. **Smith, L.C.,** Bordignon, V., Garcia, J.M. and Meirelles, F..(2000) Mitochondrial genotype segregation and effect during mammalian embryonic development: Applications to biotechnology *Theriogenology* : 35-43;
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2. Desmarais J.A., Bordignon, V., Lopes, F.L., **Smith, L.C.** and Murphy B.D. (2004) The escape of the mink embryo from obligate diapause *Biol Reprod* 70: 662-670;

3. Baqir, S. and **Smith, L.C.** (2003) Growth restricted in vitro culture conditions alter the imprinted gene expression patterns of mouse embryonic stem cells *Cloning and Stem Cells* 5: 199-212;
4. Slimane Bureau, W., Bordignon, V, Léveillée, C., **Smith, L.C.** and King, W.A. (2003) Assessment of chromosomal abnormalities in bovine nuclear transfer embryos and their donor cells. *Cloning & Stem Cells* 5: 123-132;
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38. **Smith, L.C.**, Wilmut, I. And Hunter, R.H.F. (1988) Influence of cell cycle stage at nuclear transplantation on the development in vitro of mouse embryos. *J. Reprod. Fert.* 84: 619-624.

RECENT INVITATIONS TO PRESENT AT INTERNATIONAL CONFERENCES

Name and site of event	*Title,*	*Date*
Annual Conference of the International Embryo Transfer Society, Copenhagen, Denmark ;	« Role of mitochondrial genome in preimplantation development and assisted reproductive techniques »	January, 2005
Congresso Nacional de la Sociedad Mexicana de Genética, Ixtapan de la Sal, Mexique ;	« Genetic and Epigenetic Effects on Animal Cloning and Other ARTs »	October, 2004
15th International Congress in Animal Reproduction, Porto Seguro, BA, Brazil.	« Control of xpression on Imprinted Genes in Animal Clones »	August 2004
Colloque OECD « Risk Assessment of Products from Animal Clones », Jouy en Josas, France	« Genetic and Epigenetic Alrterations to Clones : Incidence on Offspring »	November 2003
Conference on « Gametogenesis, gene Expression and human Reproduction », Guangzhou, China.	« Mitochondrial Genotype Segregation in Heteroplasmic Embryos following Nuclear Transfer »	November 2003
The 4th International Symposium on Molecular Bioengeneering of Food Animals, Osaka, Japan	« Nuclear and Cytoplasmic Remodeling after Nuclear Transfer »	May 2002
II CIBR – Ribeirão Preto, SP, Brésil	« Potential Applications of Animal Cloning and Transgenics »	September 2001
III Alpha Congress, Serono Symposium, New York, USA	« Mitochondrial Genotype Segregation in Mammals »	Septembre 2001
Workshop : Gamete function and interaction leading towards embryo development, Gent, Belgium	« Potential Applications of Animal Cloning and Transgenics »	Juin 2001
Acfas 2001 – « Promesses, défis et enjeux de la reprogrammation cellulaire », Université de Sherbrooke	« La reprogrammation de la chromatine des animaux clonés : le chemin de Dolly à Starbuck »	Mai 2001
Macdonald Symposium on Animal Production, St-Anne de Bellevue, Québec	Starbuck II and othet Potential Applications for Animal Cloning	Mars 2001
Carrefour de la biotechnologie, Hotel Marriot, Montréal, Qc	"Le clonage et le transgénisme animale: applications réeles et potentielles"	Janvier 2001
Frontiers in Reproduction Course, Marine Biological Laboratory, Woods Hole, MA	"Mitochondrial Inheritance"	June 2000
Annual Conference of the International Embryo Transfer Society, Maastrich, Pays-Bas.	"Mitochondrial genotype segregation and effects during mammalian development: applications to biotechnology"	January 2000

III Simpósio de Genética, IBILCE-UNESP, São José do Rio Preto, SP, Brésil	"Clonagem Animal: Técnicas e Aplicações"	Novembre 1999